A stochastic model of viral load and viral blips in HIV patients on ART

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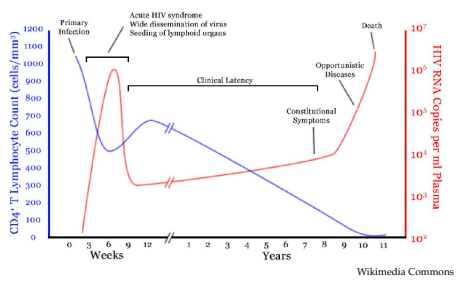
1 Introduction

Motivation

HIV primarily attacks white blood cells (CD4+)...



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- Anti-retroviral treatments (ARTs) target viral replication: ⇓ virus, ⇑ $CD4^+$
- Treatment initiation: when $CD4^+$ <350 cells/μL of blood
- However: recent evidence early treatment better!
  - Population level ⇒ ⇓ TRANSMISSION
  - Individual level ⇒ ⇑ SURVIVAL

Why not treat upon diagnosis? ⇒ POSSIBILITY OF DRUG RESISTANCE
This motivates our study of viral dynamics in patients on ART.

Understanding Viral Dynamics on Treatment

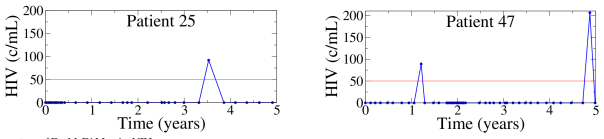
VIRAL LOAD:

- Treatment reduces viral load to <50c/mL → "undetectable"
- Mean viral load is 20-30c/mL (Dornadula et al., 1999)

Concern: Due to HIV replication? VERY error prone process - could lead to emerging drug resistance!

But: A study on structured treatment interruptions (STIs) showed that dominant virus during STIs too closely "related" to pre-treatment virus for there to be ongoing viral replication. (Joos et al., 2008)

VIRAL BLIPS: Very short periods of "detectable" viral load.



Data courtesy of Dr. M. Di Mascio, NIH

Small blips shown to be random biological and statistical variation around mean HIV-1 levels below 50 copies/mL. (Nettles et al., 2005)

Latently Infected Cells

- The HIV virus replicates in productively infected cells.
- But sometimes, after getting infected, a cell can go quiet... these are latently infected cells:
  - Not detectable by the immune system
  - Not affected by drugs, which target viral replication.
- Latently infected can later re-activate and start producing virus.

Size of Reservoir:
Differing estimates:
$0.2 - 16.8/10^6$ cells (Finzi et al., 1997)
$55 \pm 108/10^6$ cells (Fondere et al., 2003)

Lifetime of Reservoir:
Mean half-life $t_{1/2}$ =44.2 months!
Could take >70 years to eradicate.
(Siciliano et al., *Nature Medicine* (2005) amongst others.)

Question

COULD NON-ZERO VIRAL LOAD AND VIRAL BLIPS BE LARGELY ATTRIBUTABLE TO ACTIVATION OF LATENTLY INFECTED CELLS?
Consequence:
Early treatment may be safer with regards to emerging drug resistance.

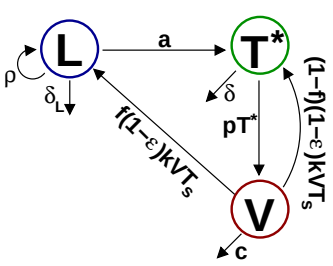
Approach

Develop a stochastic viral dynamics model that includes latent cell activation that gives a low viral load and viral blips as rare-event deviations from the mean.

2 Stochastic Viral Dynamics Model

2.1 Schematic

Let: L=latently infected cells;
T^*=productively infected cells;
V=virus.



Param.	Meaning
a	activation rate of L
ρ	replication rate of L
f	fraction of cells that become L
ε	drug efficacy
k	mass-action infection rate
T_s	"steady" number of healthy cells
δ_L	death rate of L
δ	death rate of T^*
p	production rate of V
c	clearance rate of V

2.2 Joint Probability Function

We assume the system behaves as a multi-type continuous time branching process.

Define the joint probability function

$$P_{\ell,n,v}(t) = P(L = \ell, T^* = n, V = v; t)$$

Initial condition
At $t = 0$ there are L_0 latently infected cells, T_0^* productively infected cells, and V virions. Then

$$P_{\ell,n,v}(0) = \delta_{\ell,L_0}\delta_{n,T_0^*}\delta_{v,V_0}$$

Differential Equation
We can derive a forward Chapman-Kolmogorov differential equation for the joint probability function $P_{\ell,n,v}(t)$:

$$\begin{aligned}\frac{\partial P_{\ell,n,v}(t)}{\partial t} &= a\left((\ell+1)P_{\ell+1,n-1,v} - \ell P_{\ell,n,v}\right)\\ &+ \delta_L\left((\ell+1)P_{\ell+1,n,v} - \ell P_{\ell,n,v}\right) + \rho\left((\ell-1)P_{\ell-1,n,v} - \ell P_{\ell,n,v}\right)\\ &+ f(1-\varepsilon)kT_s\left((\ell-1)P_{\ell-1,n,v+1} - \ell P_{\ell,n,v}\right)\\ &+ \delta\left((n+1)P_{\ell,n+1,v} - nP_{\ell,n,v}\right)\\ &+ (1-f)(1-\varepsilon)kT_s\left((n-1)P_{\ell,n-1,v+1} - nP_{\ell,n,v}\right)\\ &+ pn\left(P_{\ell,n,v-1} - P_{\ell,n,v}\right) + c\left((v+1)P_{\ell,v+1,n} - vP_{\ell,n,v}\right)\end{aligned}$$

This is also called a Master Equation.

NOTE: Mean behaviour of system corresponds to the deterministic model

$$\begin{aligned}M_L'(t) &= (\rho - a - \delta_L)M_L + f(1-\varepsilon)kT_SM_V\\ M_T'(t) &= (a-\delta)M_T + (1-f)(1-\varepsilon)kT_SM_V\\ M_V'(t) &= pM_T - cM_V - (1-\varepsilon)kT_SM_V\end{aligned}$$

where $M_L(t)$, $M_T(t)$, and $M_V(t)$ represent the mean # of L, T^*, and V, respectively.

2.3 Probability Generating Function

We use the differential equation for $P_{\ell,n,v}(t)$ to derive equations for the **probability generating function** (pgf).

Define the pgf $G(x, y, z; t)$ such that:

$$G(x,y,z;t) = \sum_{\ell=0}^{\infty}\sum_{n=0}^{\infty}\sum_{v=0}^{\infty} P_{\ell,n,v}(t)x^\ell y^n z^v$$

Uses of pgf $G(x, y, z; t)$:
⇒ Gives us moments

$$\text{e.g. Mean \# virions} = \sum_{\ell,n,v=0}^{\infty} vP_{\ell,n,v} = \left.\frac{\partial G}{\partial z}\right|_{x=y=z=1}$$

⇒ Gives us the probability distribution of... anything!
e.g. Individual probabilities of # of virions:

$$P(V=v) = \left.\frac{1}{v!}\frac{\partial^v G}{\partial z^v}\right|_{x=y=1,z=0}$$

We solve for the pgf numerically and use it to calculate any desired marginal or joint probability distributions.

3 Latent Reservoir Extinction

We first consider the probability of extinction of the latent reservoir.

3.1 Probability Distribution Calculation

We can obtain the cumulative probability distribution directly from the pgf: $P_{ext}(t) = P(L = 0, t) = G(0, 1, 1; t)$. The extinction probability distribution is therefore:

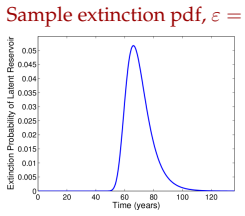
$$p_{ext}(t) = \frac{d}{dt}G(0,1,1;t),$$

which we can calculate numerically.

Special case - $\varepsilon = 1$
In the (unrealistic) case of perfect drug efficacy ($\varepsilon = 1$), latent reservoir dynamics are dictated by a single-type birth and death process which has a known analytic pgf. Therefore we have an analytic expression for the latent reservoir extinction pdf:

$$p_{ext}(t) = \frac{d}{dt}\left[\frac{(a+\delta_L)\left(1-e^{-(\rho-a-\delta_L)t}\right)}{\mu-(a+\delta_L)e^{-(\rho-a-\delta_L)t}}\right]^{L_0}.$$

Sample extinction pdf, $\varepsilon = 1$:



Mean reservoir lifetime ≈70 years
(matched to Siciliano et al., 2003)

Parameters: $c = 23\text{day}^{-1}$, $p = 20000\text{day}^{-1}$, $\delta = 1\text{day}^{-1}$, $\delta_L = 0.01\text{day}^{-1}$ (as in Kim&Perelson, 2005). a and ρ fit to match measured reservoir half-life and low viral load, $a = 5.68 \times 10^{-5}\text{day}^{-1}$, $\rho = 9.67 \times 10^{-3}\text{day}^{-1}$.

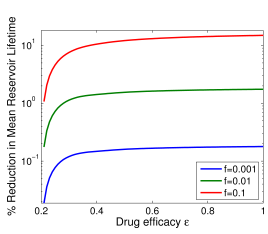
3.2 Latent Reservoir Stability

We can use our model to make predictions on the impact of improved drug efficacy on the stability of the latent reservoir. Improved drug efficacy increases the decay rate of the reservoir (Ramratnam et al., 2004).

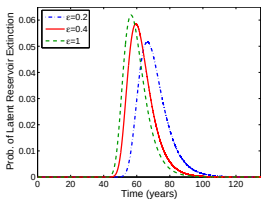
We consider the extreme case of poor drug efficacy ($\varepsilon = 0.2$) for fractions of newly infected cells becoming latent f =0.001, 0.01, 0.1.

Reduction in Lifetime
As drug efficacy improves ($\varepsilon \to 1$) the mean lifetime of the latent reservoir is decreased. However, only in the unlikely case of $f = 0.1$ is the reduction appreciable (≈15%).

Parameters as above with a, ρ fit to reservoir half-life of 60 months and low viral load for $\varepsilon = 0.2$, f =0.001, 0.01, 0.1.



3.2 Latent Reservoir Stability (cont'd)



Extinction Probability Distributions
Observe in the full extinction probability distribution (shown here for $f = 0.1$, the extreme case for illustrative purposes) that both the lifetime mean and the variance are reduced as $\varepsilon \to 1$.

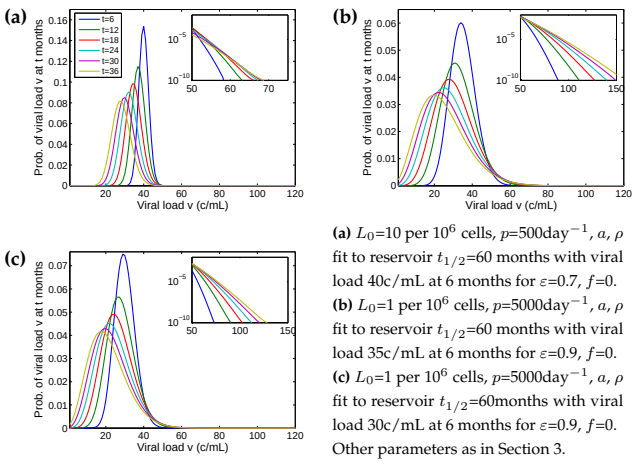
Parameters as above with a, ρ fit to reservoir half-life of 60 months and low viral load for $\varepsilon = 0.2$, $f = 0.1$.

4 Viral loads and blip probabilities

We are currently working towards fitting biologically reasonable parameters such that our model predictions are consistent with blip data.

Our hypothesis centers on the role of latent cell activation in viral load. Therefore, of particular concern is the size of the latent reservoir, for which there are different estimates (Finzi et al. 1997, Fondere et al. 2003). Below we show results for an initial latent reservoir size L_0=1 and 10 per 10^6 cells.

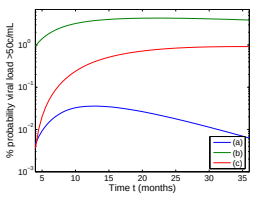
Viral load probability distributions
Below are viral load pdfs for different parameters. We pay particular attention to the tail for viral load greater than the detection level of 50c/mL (inset), which gives an the range of predicted blip sizes.



(a) L_0=10 per 10^6 cells, p=500day^{-1}, a, ρ fit to reservoir $t_{1/2}$=60 months with viral load 40c/mL at 6 months for ε=0.7, f=0.
(b) L_0=1 per 10^6 cells, p=5000day^{-1}, a, ρ fit to reservoir $t_{1/2}$=60 months with viral load 35c/mL at 6 months for ε=0.9, f=0.
(c) L_0=1 per 10^6 cells, p=5000day^{-1}, a, ρ fit to reservoir $t_{1/2}$=60months with viral load 30c/mL at 6 months for ε=0.9, f=0.
Other parameters as in Section 3.

We notice, depending on our parameters, different ranges of potential blip sizes within the span of small blips shown in Nettles et al. 2005.

Probability of a blip
We can also directly calculate the probability of a blip, $P(V > 50\text{c/mL}; t)$: the probability at time t that the viral load is greater than 50 copies/mL. The curves **(a)**, **(b)**, **(c)** correspond to **(a)**, **(b)**, **(c)** above.



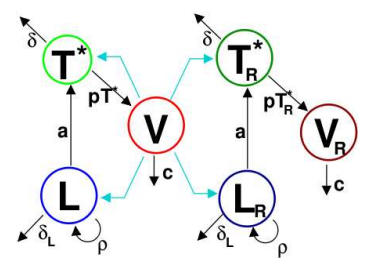
The tail of the distribution and resulting blip probabilities over time are quite sensitive to parameter choice. However, since blips are rare events, it is not obvious how to extract blip probabilities from available data. Therefore parameter regime selection remains unclear.

5 Implication - Mechanism for Drug Resistance

Model suggests that latent cell reactivation is a plausible mechanism for small viral blips. Then

- Drug resistance might *not* arise through mutation during ongoing viral replication.
- But mutants may arise during initial stages of infection (Ribeiro&Bonhoeffer, 2000) and seed the latent reservoir!

MODEL EXTENSION - FUTURE WORK:



What's new: Drug resistant latent reservoir.

6 Summary

- Stochastic model of latent cell activation in HIV+ patients shows:
  - Long-term latent reservoir extinction
  - Undetectable, non-zero viral load
  - Small viral blips (though not large viral blips)
- Now: determine parameters so model is consistent with blip data
- Next: - extend model to understand evolution of drug resistance
  - add time-dependent activation $a = a(t)$ to better model antigenic stimulation and to try to understand *large* blips.

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